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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

CYSTEAMINE 3.8 mg/mL OPHTHALMIC SOLUTION (CYSTADROPS)

(Recordati Rare Diseases Canada Inc.)

Indication: Treatment of corneal cystine crystal deposits in adults and children from two years of age with cystinosis

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AE	adverse event
BSC	best supportive care
CCCD	corneal cystine crystal deposit
CDR	CADTH Common Drug Review
CH	cysteamine hydrochloride
CUA	cost-utility analysis
ICUR	incremental cost-utility ratio
IVCM	in vivo confocal microscopy
MCID	minimal clinically important difference
QALY	quality-adjusted life-year
WTP	willingness to pay

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Cysteamine hydrochloride (Cystadrops)
Study Question	What is the cost per QALY of cysteamine hydrochloride ophthalmic solution relative to best supportive care for the treatment of corneal cystine deposits in adults and children from 2 years of age with cystinosis?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adults and children 2 years of age or older with corneal cystine crystal deposits from cystinosis
Treatment	One drop of cysteamine ophthalmic solution 3.8 mg/mL (CH 0.55%) in each eye, 4 times per day during waking hours
Outcome	Quality-adjusted life-years (QALYs)
Comparator	Best supportive care (BSC)
Perspective	Canadian public health care payer
Time Horizon	Lifetime (up to 63 years)
Results for Base Case	ICUR: $162,755 per QALY gained for cysteamine hydrochloride 0.55% vs. BSC
Key Limitations	• The model consisted of two health states (alive and dead), which does not allow adequate consideration of clinically meaningful changes that patients with cystinosis experience. The manufacturer considered only ocular components without considering other components of cystinosis which impact patients. The use of only an "alive" and "dead" state may be appropriate if a treatment is shown to impact mortality, which CH 0.55% does not. The manufacturer's model further considered only ocular components without factoring other components of cystinosis. • The manufacturer's trials do not compare CH 0.55% with BSC, and no indirect comparison was presented; thus, the comparative benefit of CH 0.55% relative to BSC remains uncertain. • The CADTH clinical review identified limitations with the clinical studies of CH 0.55% (open-label nature of the trials, validity of the outcome measures, control groups, lack of long-term data) which introduced increased uncertainty with the efficacy of CH 0.55%. • The utility and disutility values used were associated with uncertainty; the majority of the values were based on assumptions. Specifically, the baseline utility value and the disutility values for photophobia appear to overestimate the benefit of CH 0.55%. • Several clinical input assumptions made, including those related to compliance, age of entry into the model, and the likelihood and duration of band keratopathies, were not representative of clinical practice according to feedback from the clinical experts consulted by CADTH; which therefore increased the uncertainty in the results of the economic evaluation.
CDR Estimates	• CADTH could not address limitations relating to the model structure or comparative effectiveness of CH 0.55% with BSC. • CADTH conducted reanalyses, using a baseline utility value deemed more representative of the trial data and the Canadian population; alternate disutility values for photophobia and blindness; age at model entry based on trial data; a lower compliance rate; removal of incidence of band keratopathy; and updated vision loss costs to reflect the payer perspective. • The revisions resulted in CADTH's base-case ICUR of $736,828 per QALY gained for CH 0.55% vs. BSC. A price reduction of more than 80% was required to achieve an ICUR below $100,000 per QALY.

BSC = best supportive care; CDR = CADTH Common Drug Review; CH 0.55% = cysteamine hydrochloride 0.55%; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-years.

Drug	Cysteamine hydrochloride ophthalmic solution (Cystadrops)
Indication	Treatment of corneal cystine deposits in adults and children from 2 years of age with cystinosis
Reimbursement Request	As per indication
Dosage Forms	Solution / 3.8 mg/mL
NOC Date	February 11, 2019
Manufacturer	Recordati Rare Diseases Canada Inc.

Executive Summary

Background

Cystinosis is a rare, hereditary disease characterized by the accumulation of cystine crystals in all cells and tissues. The two earliest manifestations of cystinosis are renal dysfunction leading to end-stage renal disease and accumulation of corneal cystine crystal deposits (CCCDs) resulting in photophobia. The most severe form of cystinosis, infantile nephropathic cystinosis, makes up approximately 95% of cystinosis cases.[1,2] CCCDs in these patients are typically observable by 18 months of age and photophobia from corneal deposits appears in about 50% of patients from mid-childhood to adolescence.[3] Juvenile or intermediate renal cystinosis is diagnosed in late childhood or adolescence and is associated with a slower progression of symptoms than in infantile cystinosis.[1,3] Ocular or non-nephrotic cystinosis is characterized by adult onset with CCCD as the only manifestation.[1]

Cysteamine hydrochloride (CH) 0.55% (Cystadrops) is an ophthalmic solution indicated for the treatment of CCCDs in patients two years of age or older with cystinosis. The recommended dose for CH 0.55% is one drop of solution in each eye, four times per day during waking hours.[4] CH 0.55% is available in 5 mL vials containing 3.8 mg/mL cysteamine, which must be replaced every seven days.[4] At a price of $1,986 per vial, the annual cost per patient is $103,272. The manufacturer's reimbursement request was as per indication.[5]

The manufacturer submitted a cost-utility analysis comparing CH 0.55% (four drops in each eye every day) to best supportive care (BSC), which was described as symptomatic treatment and supportive care for ophthalmic events (e.g., ophthalmologist visits and procedural costs), in patients two years of age or older with CCCDs due to cystinosis.[6] The model was conducted from the Canadian public health care payer perspective over a lifetime time horizon of up to 63 years (average 25 years). Future costs and benefits were discounted at a rate of 1.5% per year. The submitted model was in the form of a cohort-level Markov model, with two health states: "alive" and "dead." The model focused on the ocular components of cystinosis and did not consider the non-ocular components of cystinosis, assuming that there would be no differences between treatments for these components. While in the "alive" health state, patients could experience ophthalmic events that represented disease worsening, such as photophobia, visual impairment, band keratopathies, blepharospasm, filamentary keratitis, and corneal vascularization. Patients could experience one or more of these events during each three-month cycle. Event probabilities for patients receiving CH 0.55% were derived from results of the "CH for

nephrOpathic Cystinosis" (CHOC) study,[7] while a mix of natural history data and clinical expert input was used to inform the BSC arm of the model.[6] All patients entered the model in the "alive" state in near perfect health and disutilities were applied for each ophthalmic event, based on either published literature or consultation with a clinical expert.[6] Treatment costs were incorporated based on the manufacturer's submitted drug price and management of disease related costs were incorporated based on a mixture of feedback from clinical experts for resource use and costing from the Ontario Ministry of Health and Long-Term Care Schedule of Benefits.[6]

In the manufacturer's base case, CH 0.55% was associated with an incremental cost of $1.9 million with a gain of 11.77 quality-adjusted life-years (QALYs) when compared with BSC. The resulting incremental cost per QALY gained for CH 0.55% versus BSC was $162,755. The manufacturer reported the ICUR was below a willingness to pay of $100,000 per QALY in approximately 16% of iterations.[6]

Summary of Identified Limitations and Key Results

CADTH identified several key limitations with the manufacturer's economic evaluation. First, the manufacturer did not adhere to best modelling practices.[8] The model structure consisted of two states, "alive" and "dead," which does not allow adequate consideration of clinically meaningful changes that patients with cystinosis experience, and appears to assume the treatment has an impact on mortality; which CH 0.55% does not. The manufacturer considered only ocular components of the condition in the model, and did not consider the underlying disease that is present in the majority of cystinosis patients: nephropathic cystinosis. In not considering the ophthalmic complications in the context of the underlying condition, the manufacturer appears to overestimate the total amount of QALYs patients with cystinosis experience in the context of the underlying disease,[9] and likely overestimated the QALY benefits associated with CH 0.55%.

The previously identified limitation regarding the relative impact of ophthalmic complications on patient quality of life was further affected by the application of utility values and disutilities in the model. The baseline utility value in the model was 1 (i.e., perfect health), which is inappropriate given most patients with nephropathic cystinosis are likely experiencing some morbidity beyond mild photophobia and are thus not in perfect health (Canadian general population utility values are approximately 0.86).[10] Additionally, the values for many of the disutilities applied within the model for ophthalmic events were obtained via consultation with clinical experts and not using standardized elicitation methods on patients. While there may be a paucity of evidence for this condition, this method for eliciting data introduces increased uncertainty to the estimates. A key driver of the model results was disutility for photophobia; in which each increase in grade of severity on a five-grade scale was estimated to decrease patient quality of life by a score of 0.1. Feedback from clinical experts consulted by CADTH confirmed this was unlikely to be a valid assumption, as grade 5 photophobia would not warrant such a decrease in quality of life relative to other common cystinosis complications. Overall, these sources of uncertainty with utilities likely overestimated the burden of ophthalmic complications of cystinosis on quality of life, biasing results in favour of CH 0.55%.

CADTH also considered the comparative efficacy of CH 0.55% when compared with BSC to be uncertain. The manufacturer used data from the CHOC trial which compared CH 0.55% to an active comparator (CH 0.1%), while making assumptions for BSC as there were no data comparing CH 0.55% to BSC.[7,11] Further, the CADTH clinical review noted that the validity, reliability, and minimal clinically important difference of the photophobia scales are

unknown and that there was a risk of bias in these scales due to their subjective nature, as well as the open-label trial design, and as such conclusions could not be drawn. CADTH reviewers also highlighted that the long-term effectiveness of CH 0.55% remains uncertain. As a result, the assumption that clinical benefit of CH 0.55% is maintain may overestimate the benefit of CH 0.55%, which would bias the cost-effectiveness results in its favour.

Furthermore, the clinical experts consulted by CADTH provided feedback that several assumptions relating to clinical inputs were not representative of Canadian clinical practice. The manufacturer assumed patients would be 100% compliant on treatment, would begin treatment at two years of age (and that the trial data are representative of this), and could experience band keratopathies, which were assumed to be permanent. These assumptions were considered unlikely to be reflective of clinical practice in Canada, as patients in their clinical practices have low compliance with eye drops, patients would likely start on treatment only if they were symptomatic, which typically would be later than two years of age, and none of the experts' patients with cystinosis had developed band keratopathies. Finally, the manufacturer's modelling assumptions did not allow patients receiving CH 0.55% to reach level 5 photophobia. These assumptions led to the relative clinical benefit being overestimated.

CADTH also identified additional limitations with the manufacturer's model: the manufacturer excluded treatment-related adverse events from their model despite the product monograph indicating several potentially important treatment-related adverse events; costs not appropriate for the payer perspective were used; and, inappropriate alpha and beta calculations were used to define the beta distributions for the probabilistic analyses.

The CADTH base case addressed the identified limitations, as possible, by incorporating a revised patient starting age to reflect the mean age of patients in the clinical trial (17 years of age) in line with the clinical data, applying a different baseline utility value, reducing the disutility associated with photophobia, reducing the disutility for vision loss, reducing patient compliance, removing the probability of experiencing band keratopathy, removing inappropriate vision loss costs and applying appropriate calculations for alpha and beta values. CADTH's base case resulted in incremental costs of $1.7 million and incremental QALYs of 2.34 for an ICUR of $736,828 per QALY gained. CADTH undertook a scenario analysis with a starting age of 2 years, though this requires a strong assumption that the data observed in a subgroup of the trial participants (patients aged 2 to 17 years) are generalizable to patients aged 2 years. In this population, the ICUR was estimated to be $520,360 per QALY. While this population is more aligned with the Health Canada indication, this analysis is associated with greater uncertainty than the CADTH base case.

Conclusions

CADTH's base case reported that CH 0.55% was associated with an ICUR of $736,828 per QALY gained compared with BSC for treatment of CCCD in patients with cystinosis. Price reductions of more than 80% and 87% were required to achieve ICURs below $100,000 and $50,000 per QALY, respectively.

However, given the limitations with the submitted model structure, the limited amount of available comparative data and the strong reliance on assumptions, the results should be viewed with caution, especially when considering the potential impact of this product in the overall clinical condition of patients with cystinosis.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis which compared cysteamine hydrochloride (CH) 0.55% versus best supportive care (BSC) (i.e., current symptomatic care – accruing health state and symptom treatment costs of ophthalmic events [e.g., ophthalmologist visits and procedural costs] only) in patients two years of age or older with CCCDs from cystinosis. The analysis was conducted over a lifetime time horizon (up to 63 years) from the Canadian public health care payer perspective with a discount rate of 1.5% applied to costs and QALYs.

The model structure consisted of two health states: "alive" and "dead." In the "alive" state, patients could experience the following ophthalmic events during each three-month cycle: photophobia, visual impairment, band keratopathies, blepharospasm, filamentary keratitis, and corneal vascularization. Baseline characteristics were derived from one open-label, parallel-group, phase III randomized controlled trial, the "CH for nephrOpathic Cystinosis" (CHOC) study.[7] All patients entered the model in the "alive" state at two years of age. No patients had visual impairment, and none had experienced band keratopathies, or corneal vascularization; though 27% had experienced blepharospasm and 3% had experienced filamentary keratitis. At model entry, patients had an average cystine crystal density, identified via in vivo confocal microscopy (IVCM), of 9.82 and a photophobia score of 1.37 (on a scale from 0 to 5).[6] These data were based on a pediatric subset of the CHOC trial (defined as < 18 years, n = 38). Every three months following entry into the model, patients either remained in the "alive" state, and potentially experience ophthalmic events, or moved to the absorbing death state. The probability of moving into the death state was based on Canadian life tables[12] that were adjusted by a standardized mortality ratio to reflect the significantly reduced life expectancy (median age: 40) for cystinosis patients.[13]

Treatment efficacy was applied to patients receiving CH 0.55% through the probability of experiencing ophthalmic events. The manufacturer assumed that patients receiving CH 0.55% did not experience any ophthalmic events based on the conclusions of the CHOC trial, except for low-severity photophobia. In the CHOC trial, patients on CH 0.55% did not experience any increase in CCCDs and these values remained stable over the duration of the trial. Because it was assumed CCCD density was directly related to the probability of experiencing the ophthalmic events listed above, patients on CH 0.55% did not experience any ophthalmic events. Risks of ophthalmic events for patients not on treatment were obtained from a combination of published literature and clinical expert opinion. This was necessary as the comparator group in the CHOC trial received an active treatment and no data for BSC; the manufacturer's comparator in the economic evaluation, could be obtained from the trials. No treatment-related adverse events were included in the model.

Disutility values for photophobia,[5] blepharospasm, band keratopathies, filamentary keratitis, and corneal vascularization were obtained from global key opinion leaders,[13] while the utility decrements for visual impairment were obtained from a previously published cost-effectiveness analysis assessing screening for age-related macular degeneration.[14] The following resource use and costs were also included in the model: cost of CH 0.55% therapy, background medical management, and ophthalmic-outcome related costs. Background medical management consisted of ophthalmologist visits,[15] with patients on

treatment requiring half the number of visits as those receiving BSC. Costs for these visits were obtained from the Ontario Schedule of Benefits and Physician Services.[16] Resource use and costs for band keratopathies, blepharospasm, and debridement of filaments were based on feedback from a key opinion leader.[5] Costs related to visual impairment was obtained using the average direct medical and non-medical cost of visual impairment across all stages in Canada[17] and adjusting this value by the percentage of the average cost which relates to each level of visual impairment[18] to obtain impairment-level severity specific costs.

Manufacturer's Base Case

In the base case, the manufacturer reported that CH 0.55% was associated with an incremental cost of $1.9M compared with BSC, and was associated with an additional 11.77 QALYs over the lifetime time horizon. This resulted in an incremental cost per QALY of $162,755 for CH 0.55% versus BSC (Table 10).The ICUR was below a willingness to pay of $100,000 per QALY in approximately 16% of iterations.

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted a number of one-way sensitivity analyses and scenario analyses to determine what the model drivers were and to test alternative assumptions, Table 11. The model was most sensitive to the treatment effects on visual impairment, the disutility value used for photophobia and the starting population age. When no treatment effect on visual impairment was applied, the ICUR rose to $280,674 per QALY. When the disutility for each increase in grade severity for photophobia was reduced from 0.1 to 0.05 per grade, the ICUR rose to $243,412 per QALY. When age upon entry into the model was altered to reflect a mixed population of adults and pediatric patients starting treatment using the mean age from CHOC trial, the ICUR rose to $343,048 per QALY.

Limitations of Manufacturer's Submission

- **Model structure does not appropriately capture the clinical disease pathway:** An appropriate model structure for a given economic evaluation should capture a relevant and meaningful underlying clinical or biological process. The model submitted by the manufacturer consisted of two states, alive, and dead. This model structure may not appropriately capture the natural progression of ocular cystinosis or the impact of treatment efficacy, given CH 0.55% has no impact on survival, and several consequences of CCCDs which the treatment aims to prevent were captured as events within the alive state, though not explicitly modelled. Additionally, the manufacturer did not consider the underlying disease, nephropathic cystinosis, that the majority of patients would have and the impact this disease has on quality of life over time, relative to the impacts of ocular complications. Also, of note, the manufacturer did not allow for consideration of treatment discontinuation within the model. Finally, many of the events in the model were based on the in vivo confocal microscopy (IVCM) score, which may not be appropriate. Clinical experts consulted by CADTH indicated the IVCM does not necessarily correlate with vision loss and other ophthalmic events, and thus it is difficult to interpret the clinical significance of a change in patient's corneal images on such events. As a result of these limitations, there is substantial uncertainty with the manufacturer's model, though these limitations could not be addressed within the CADTH reanalyses.
- **Benefit of CH 0.55% compared with BSC is uncertain:** The manufacturer's trials for CH 0.55% used an active comparator (CH 0.1%) and thus, there is no comparative data for CH 0.55% compared with BSC, the only comparator in the manufacturer's submitted

economic evaluation. The manufacturer based the natural history of disease in the absence of treatment (i.e., BSC) on input from clinical experts in the absence of data, and assumed patients not receiving treatment would experience an annual increase in IVCM of 0.1, while assuming IVCM remained stable for patients on CH 0.55% based on the conclusions of the CHOC trial.[7] This may not be appropriate, as the clinical report conducted by CADTH noted there was limited evidence for the association of IVCM total score with symptoms, as demonstrated by weak correlations with patient- and investigator rated photophobia scales. The manufacturer mapped photophobia severity to increase in IVCM in the model. Given the importance of this parameter within the model, the magnitude of benefit associated with CH 0.55% when compared with BSC may be overestimated if less than 100% compliance is assumed.

- **Efficacy of CH 0.55% is uncertain:** The CADTH clinical review noted that the validity, reliability, and minimal clinically important differences (MCIDs) of the photophobia scales are unknown and that there was a risk of bias in these scales due to their subjective nature and the fact that the CHOC study was open-label. While some benefit of CH 0.55% compared with CH 0.1% was observed in terms of IVCM total score and other measures of corneal cystine crystal burden, the MCIDs for these measures are unknown and there is limited evidence for associations between these measures and patient-important outcomes. There was a potential risk of bias in IVCM total score due to the lack of blinding of the investigators acquiring and selecting the images for rating which contributed some uncertainty to the magnitude of the treatment effect. Additionally, the long-term effectiveness of CH 0.55% remains uncertain, as the primary end point of the CHOC trial was 90 days, and the single arm OCT-1 trial, which contained data on eight patients for 60 months, had no control group, which meant conclusions could not be drawn regarding long-term efficacy of CH 0.55%.[7,11] This is an important issue given CH 0.55% is assumed to be a lifetime treatment and the manufacturer claims cystine crystal deposition in the cornea will remain stable indefinitely, based on IVCM score remaining stable in the CHOC (90 day) and OCT-1 (60 month) trials, thus preventing any ocular complications over a patient's lifetime. As a result, patients are assumed to never discontinue CH 0.55%. None of the issues related to CH 0.55% treatment efficacy could be appropriately addressed in the CDR reanalyses.
- **Baseline utility input is overestimated:** The baseline utility applied in the model was for near perfect health, with only some disutility at baseline due to mild photophobia. This is not appropriate given the majority of patients indicated for use of CH 0.55% have underlying nephropathic cystinosis and have non-ocular consequences of disease that likely impact their quality of life. This would indicate they are further below perfect health than is depicted at baseline. The application of this value over the lifetime time horizon, as long as patients did not experience ocular events further exacerbations, overestimates the actual quality of life that patients with cystinosis experience. To address this issue, a baseline utility value of 0.86 was identified in the literature as the mean value for adults in Canada and applied.[10] This also aligns with the value used in the CADTH review of cysteamine bitartrate in a population of patients aged ~2 years. Several other disutility values, including that for blindness, were adjusted in the CADTH base case to reflect the relative change in baseline utility value.

- **Application of disutilities is highly uncertain:** Disutilities were applied within the "alive" state for ophthalmic events. Many of the disutilities identified by the manufacturer were obtained via consultation with clinical experts and not from validated measures used to determine utilities. The value for photophobia in particular, estimated based on clinical expert opinion, was determined to lead to a disutility of 0.1 per photophobia grade (and incremental decrements were applied to changes by fractions of grade, e.g., score of 1.5 results in a utility decrement of 0.15). When using the manufacturer's baseline utility of 1, having grade 5 photophobia alone (a disutility of 0.5), would lead to a 50% decrease in quality of life. As mentioned earlier, most patients receiving CH 0.55% would have nephropathic cystinosis and experience other chronic, non-ophthalmic issues which have a significant impact on quality of life. The clinical experts consulted by CADTH indicated such a disutility does not meet face validity, as they would consider such a large decrease in quality of life to be debilitating, yet they do not anticipate grade 5 photophobia to warrant such a decrease relative to other cystinosis related issues. One of the clinical experts also noted that some patients do not receive treatment for their photophobia symptoms; hence photophobia is unlikely to warrant such a significant impact on quality of life. The disutility for photophobia was reduced to 0.025 per grade in the CADTH base case to address this limitation, and 0.05 was tested in a scenario analysis.

  Furthermore, the disutilities were applied using an additive approach, when a multiplicative approach would have been more appropriate to avoid overestimating the impact of multiple disutilities on a health state. This additive approach is likely to have overestimated the impact of ophthalmic events in patients not receiving treatment since these events did not apply to patients on CH 0.55%, biasing results in favour of CH 0.55%. Once CADTH undertook revisions to the utility and disutility assumptions, this had less of an impact on the results.
- **Clinical input assumptions not representative of clinical practice:** The manufacturer made several assumptions relating to clinical inputs, particularly those for compliance, the starting population age, age at which grade 5 photophobia would be reached, and probability and duration of band keratopathies that are not representative of clinical practice.
  - **Compliance:** In their base case, the manufacturer assumed patients on CH 0.55% would be 100% compliant. Based on feedback from the clinical experts consulted by CADTH, this is not representative of clinical practice and very unrealistic. In their estimation, compliance is estimated to be much lower in general based on the frequent (four times per day) dosing regimen for CH 0.55%. Children are likely to have good compliance, whereas adults are likely to be less compliant. Compliance has an impact on treatment efficacy, as patients will only receive the full benefit from CH 0.55% if they are fully compliant. As a result, this assumption overestimates the benefit associated with CH 0.55%. To address this limitation, a compliance rate of 75% was applied in the CADTH base case.
  - **Mean age of patients entering the model:** Patients entered the model at 2 years of age in the manufacturer's base case. Based on feedback from the clinical experts consulted by CADTH, patients would be treated for CCCDs once they become symptomatic, which may occur at much more advanced ages. Additionally, the mean age of patients in the CHOC trial were not aligned with this patient starting age.[7] This limitation could potentially lead to the overestimation of the clinical benefit associated with CH 0.55% and bias results in its favour. The mean age from the CHOC trial was applied in the CADTH base case in order to address this limitation.

Two scenario analyses (lifetime time horizon and 20-year time horizon) with the patient starting age set to two were also conducted.

  - Changing this setting within the model has a subsequent impact on the estimated photophobia score of patients. As submitted, patients at age 17 would have a photophobia score of 4.4, which is not in line with the full-patient population in the CHOC trial, where patients had a baseline photophobia score of 1.77. CADTH applied the correct baseline photophobia score of 1.77 and respective decrease after three months (0.63) in the CADTH base case and all scenarios with the patient starting age based on that of the CHOC trial. These values were reverted back for all scenarios where patient starting age was two.
  - **Band keratopathy:** The manufacturer included a probability of band keratopathy for patients not on treatment in their base-case analysis, and assumed the quality of life impact would be permanent. Feedback from one of the clinical experts consulted by CADTH indicated band keratopathies are not permanent, and the clinical expert also noted none of their patients had experienced them. Their inclusion within the manufacturer's base case increased costs and reduced QALYs for patients not on treatment, biasing results in favour of CH 0.55%. Probability of band keratopathy was removed from the CDR base case to address this limitation.
  - **Modelling of photophobia:** The manufacturer assumed all patients would reach extreme photophobia (grade 5) at the age of 20 in the BSC arm of the economic evaluation. Clinical experts consulted by CADTH noted not all patients reach extreme photophobia, indicating this assumption is not representative of clinical practice, or that clinical practice has evolved since the manufacturer's source for this assumption in 2003. The manufacturer's assumption that patients who were compliant on CH 0.55% could not experience photophobia in the model (while non-compliant or BSC patients could experience photophobia, albeit at different rates) was uncertain and biased results in favour of CH 0.55%. To address the uncertainty around this issue, the age at which patients reached extreme photophobia was set to 50 years of age, the maximum allowable setting in the model, in a scenario analysis to better reflect that not all patients experience extreme photophobia, while alternate compliance was also tested. Additionally, based on the manufacturer' s programming in the model, the maximum photophobia score for patients receiving CH 0.55% was always below 5 (typically between 3 and 3.5 based on the analyses undertaken). This is not representative of clinical practice and biases results in favour of CH 0.55%. CADTH could not address this limitation and thus its impact remains uncertain.

- **Exclusion of treatment-related adverse events:** The manufacturer did not incorporate any treatment-related adverse events within the model. The product monograph lists eye pain, blurred vision, eye irritation, and eye pruritus among common adverse events with CH 0.55%. Such events should have been incorporated in the model and their exclusion leads to an overestimate of the benefit associated with CH 0.55%. These adverse events could not be incorporated in the CADTH reanalyses and thus their impact on cost-utility estimates for CH 0.55% remains uncertain.
  - One note of clarification with regards to treatment-related adverse events is necessary. In the pharmacoeconomic report submitted by the manufacturer, events related to treatment efficacy are referred to as adverse events. These ophthalmic events are part of the natural progression of CCCDs from cystinosis if left untreated and are thus not adverse treatment events.

- **Inappropriate derivation of beta distributions:** The probabilistic results varied between different model runs, and upon further inspection, CADTH identified the beta distributions for certain parameters as the source of the instability. The random draws around these distributions frequently pulled values that fell beyond the 95% confidence interval defined by the distribution as defined by the manufacturer. The alpha and beta values used to define the beta probability distributions in the manufacturer's submission were calculated using the method for count data, but the inputs to which they referred were continuous measures. Continuous measures with beta distributions require a different method using the mean and standard deviation to generate alpha and beta values. The correct derivation method for alpha and beta values for beta distributions were applied in the CADTH reanalyses.
- **Generalizability of results to Canadian clinical practice uncertain:** Feedback from a clinical expert consulted by CADTH indicated patients may be receiving off-label topical treatment for their CCCDs. The model currently depicts patients switching from BSC to CH 0.55%, but in reality many would actually be switching from a similar treatment, compounded CH, to CH 0.55%. As a result of this information, the model may not appropriately depict current clinical practice, and model results are uncertain.
- **Inappropriate costs for vision loss applied:** Costs from productivity losses and dead weight losses from transfers including welfare payments and taxations forgone, among other cost categories, were included in the annual visual impairment costs applied to the manufacturer's model. These costs fall outside the public health care payer perspective and should not be incorporated in the base-case analysis. This overestimates the costs from no treatment and biases results in favour of CH 0.55%. The value identified from the literature by the manufacturer should have been $10,570 per person, with vision loss per annum after removing productivity loss and loss of well-being costs, and not $19,370 as was used in the manufacturer's base case. This revised value was applied in the CADTH base case.

CADTH Common Drug Review Reanalyses

CADTH conducted reanalyses to address some of the limitations listed above, which included:

1. Changing the starting age of the population to "mixed"(17 years of age) instead of "pediatric" (two years of age) to reflect the full CHOC trial population [no stratified population data were identified in the CADTH clinical review].
2. Applying the CHOC trial values for baseline photophobia for all patients (as opposed to the "pediatric" subset).
3. Altering patient compliance on CH 0.55% from 100% to 75%.
4. Changing the baseline utility value from 1 to 0.86.
5. Reducing the disutility for each additional grade severity of photophobia from 0.1 to 0.025.
6. Removing the occurrence of band keratopathy from the model.
7. Reducing the disutility for blindness from 0.54 to 0.40 to reflect the lower baseline utility value used in the CADTH base case.
8. Reducing the annual cost of visual impairment was updated to exclude productivity loss and dead weight losses from transfers including welfare payments and taxation forgone, among other cost categories not relevant to the public payer perspective, from $19,370 per year to $10,570.

9. Applying the appropriate method for deriving alpha and beta values to determine value ranges for probabilistic inputs using beta distributions.

Results of the reanalyses are presented in Table 2. The single parameter changes that most heavily impacted the model results were the change in the starting population age, which decreased the incremental QALYs and resulted in an incremental cost per QALY of $375,285, and the reduction in photophobia disutility to 0.025 per grade, which resulted in much higher total QALYs for patients on BSC, resulting in an ICUR of $316,706 per QALY gained.

CADTH's base case combined each of the one-way analyses and resulted in a decrease in in total costs ($2,317,961) and QALYs (12.52) for CH 0.55%, and a reduction in total costs ($596,427) and small decrease in total QALYs (10.18) for BSC. This resulted in an ICUR of $736,828 per QALY gained. The probability that CH 0.55% was cost-effective if a decision-maker's willingness to pay was no more than $600,000 per QALY gained was 3.7%.

Table 2: CDR Reanalyses

			Total Costs	Incremental Cost of CH 0.55%	Total QALYs	Incremental QALYs of CH 0.55%	Incremental Cost per QALY
	Base case	BSC	$714,216		11.92		
		CH 0.55%	$2,630,341	$1,916,126	23.70	11.77	$162,755
1.	Starting age of population is set to 17 (representative of the trial population)	BSC	$906,682		4.73		
		CH 0.55%	$2,534,176	$1,627,494	9.06	4.34	$375,285
2.	Correction of photophobia scores based on full CHOC trial population	BSC	$715,063		11.17		
		CH 0.55%	$2,629,528	$1,914,465	22.50	11.33	$168,965
3.	75% Compliance	BSC	$714,842		11.17		
		CH 0.55%	$2,711,896	$1,997,054	22.30	10.53	$189,592
4.	Baseline utility is 0.86	BSC	$714,155		7.95		
		CH 0.55%	$2,627,791	$1,913,635.60	20.14	12.19	$156,981
5.	Photophobia disutility is 0.025 per grade	BSC	$714,497		18.96		
		CH 0.55%	$2,629,047	$1,914,550	25.01	6.05	$316,706
6.	No band keratopathies	BSC	$714,161		12.68		
		CH 0.55%	$2,628,667	$1,914,505	23.69	11.01	$173,962
7.	Disutility for blindness changed to 0.4 from 0.54	BSC	$2,630,022		11.46		
		CH 0.55%	$1,915,620	$714,402.20	23.66	12.19	$157,103
8.	Visual impairment costs fixed	BSC	$394,157		11.66		
		CH 0.55%	$2,629,619	$2,235,462	23.71	12.05	$185,585
9.	Appropriate calculation of alpha and beta values for Beta distributions	BSC	$714,605		11.56		
		CH 0.55%	$2,629,293	$1,914,688	23.69	12.13	$157,841
	CADTH Base Case (combining 1-9)	BSC	$596,427		10.18		
		CH 0.55%	$2,317,961	$1,721,534	12.52	2.34	$736,828

BSC = best supportive care; CH 0.55% = cysteamine hydrochloride 0.55%; QALY = quality-adjusted life-year.

Note: The model results were generally stable over multiple model runs.

Several scenario analyses were undertaken to consider alternate scenarios from those in the CADTH base case, but using the CADTH base case as the basis for the analysis (Table 12):

a) Patient populations starting at two years of age with a lifetime time horizon, based on manufacturer's original assumption. This included reverting to the use of a photophobia score of 1.37 at baseline which resulted in a score of 4.40 at age 17.
b) Patient population starting age of 2 years of age with a 20-year time horizon. This included reverting to the use of a photophobia score of 1.37 at baseline which resulted in a score of 4.40 at age 17.
c) Compliance set to 100%, as opposed to 75%.
d) Compliance set to 50%, as opposed to 75%.
e) The disutility for each additional grade severity of photophobia was altered from 0.025 to 0.05.
f) Grade 5 photophobia was assumed to be reached in patients not on therapy after 50 years post-treatment and not 20.

Of particular interest are the scenarios relating to a population starting age two, as the clinical experts consulted by CADTH noted younger patients might be a subgroup more likely to benefit from treatment than older patients with cystinosis, and that some clinicians may want to start their patients on CH 0.55% before they are symptomatic. In the scenario with a lifetime time horizon, the ICUR decreased to $520,360 per QALY gained when compared with the ICUR from the base case ($736,828). When the time horizon was limited to 20 years, the ICUR rose to $808,969 per QALY gained. This is important to note given many of the events driving the difference in QALYs between CH 0.55% and BSC within the model, occur at a later stage beyond 20 years, stages for which we do not have any efficacy data. Increasing the impact of each grade of photophobia from –0.025 per grade to –0.05 per grade resulted in an ICUR of $439,573 per QALY gained; while delaying the age of onset of grade 5 photophobia, increased the ICUR to $985,025 per QALY gained.

CADTH undertook an exploratory analysis in an attempt to address uncertainty with the coding of the photophobia score for patients on CH 0.55% in the manufacturer's original submission, when the population starting age was set to "mixed." The results of an analysis using the originally submitted values on the CADTH base case are presented in Appendix 4.

CADTH undertook a price-reduction analysis based on the manufacturer submitted and CADTH base-case analyses, assuming proportional price reductions for CH 0.55% (Table 3). A price reduction of greater than 80% would be required to reach a willingness to pay of $100,000 per QALY gained.

Table 3: CDR Reanalysis Price-Reduction Scenarios

ICURs of Submitted Drug Versus Comparator		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CDR**
Submitted	$162,755 per QALY	$736,828 per QALY
10% reduction	$136,330 per QALY	$656,962 per QALY
20% reduction	$114,084 per QALY	$576,694 per QALY
30% reduction	$94,245 per QALY	$499,057 per QALY
40% reduction	$71,463 per QALY	$417,344 per QALY
50% reduction	$49,313 per QALY	$338,749 per QALY
60% reduction	$27,415 per QALY	$259,932 per QALY
70% reduction	$6,229 per QALY	$180,066 per QALY
80% reduction	NA	$101,432 per QALY
90% reduction	NA	$22,707 per QALY

CDR = CADTH Common Drug Review; NA = not applicable; QALY = quality-adjusted life-year.

Issues for Consideration

- Feedback from one of the clinical experts consulted by CADTH indicated that patients may be receiving compounded oral cysteamine for their CCCDs through hospitals or compounding pharmacies. The model currently depicts patients switching from BSC to CH 0.55%, but, in reality, many patients would actually be switching from an active treatment, compounded CH (0.1% to 0.55%) to CH 0.55%. As per Health Canada guidelines, "compounding should only be done if there is a therapeutic need or lack of product availability and should not be done solely for economic reasons for the health care professionals."[19] With the availability of CH 0.55%, compounded cysteamine should not be used, justifying its exclusion as a comparator. However, the generalizability of the economic evaluation with current clinical practice is uncertain.
- The annual cost of currently available compounded cysteamine is paid by patients out of pocket, according to feedback from clinical experts consulted by CADTH. The clinical experts also noted there is no standardized preparation across Canadian practice, and some patients may not have access based on proximity to pharmacies with compounding capabilities.
- Data from a case series noted no improvement in cystine crystal deposit density upon use of hospital-pharmacy compounded CH drops (0.55%).[13] They noted that the lack of efficacy may have to do with compliance and difficulty with the storage requirements, as well as the time lag between when diagnosis was first made and when the drops were first used.
- Feedback from clinical experts consulted by CADTH indicated most patients receiving CH 0.55% will also be receiving systemic, oral delayed-release cysteamine for nephropathic cystinosis, which has an associated annual treatment cost between $136,109 (children 2 years of age) and $321,711 (for adults).
- CH 0.55% is expected to only impact the cornea, though cystine crystal deposits can occur in other segments of the eye and lead to visual impairment, particularly the retina. As noted above, patients will likely be taking oral cysteamine bitartrate for nephropathic cystinosis, and clinical expert feedback suggests oral treatment for cystinosis has an additional benefit on the retina in these patients. However, CADTH notes this does not

align with the CADTH clinical review for cysteamine bitartrate, as no data relating to impact of oral cysteamine on ophthalmic events was identified. As a result, this remains uncertain.

- Behaviours in compliance may vary with age, as well as frequency of dosing, according to clinical experts consulted by CADTH. They noted teens in particular are less likely to be compliant. Currently available treatments may require more frequent dosing when compared with CH 0.55%. This is of note given the impact of compliance on treatment efficacy.

Patient Input

As noted in the CADTH clinical review, no patient input was received specifically for CH 0.55%.

As per the CADTH clinical review, patient input received for the review of cysteamine bitartrate (Procysbi) was reviewed and no information was provided regarding experience with the treatment of corneal cystine deposits. The patient input provided did note that deficits in eye sight were among the important challenges not addressed by currently available systemic treatments. Additionally, patients are concerned with the high costs of treatment typically associated with cystinosis therapies, as well the burden of frequent dosing regimens. The latter point may play a role in patient compliance and subsequent treatment efficacy.

Conclusions

CADTH's base case reported that CH 0.55% was associated with an ICUR of $736,828 per QALY gained compared with BSC for treatment of CCCDs in patients with cystinosis. Price reductions of more than 80% and 87% were required to achieve ICURs below $100,000 and $50,000 per QALY, respectively.

However, given the limitations with the submitted model structure, the limited amount of available comparative data and the strong reliance on assumptions, the results should be viewed with caution, especially when considering the potential impact of this product in the overall clinical condition of patients with cystinosis.

Appendix 1: Cost Comparison

The comparators presented in the Table 4 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 4: CDR Cost Comparison Table for the Treatment of Corneal Cystine Deposits in Cystinosis

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Cysteamine (Cystadrops)	3.8 mg/mL	Ophthalmic solution	$1,986.0000 per 5 mL vial	One drop in each eye, 4 times per day during waking hours, not exceeding 4 drops per eye each day	283.71	103,272[a]

Note: Based on manufacturer submitted price.[5]

[a] Assumes one vial per week, with any unused solution discarded after 1 week according to the product monograph.[4]

Appendix 2: Summary of Key Outcomes

Table 5: When Considering Only Costs, Outcomes and Quality of Life, How Attractive Is Cysteamine Hydrochloride 0.55% Relative to Best Supportive Care?

CH 0.55% Versus BSC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio	$736,828 per QALY					

CE = cost-effectiveness; BSC = best supportive care; CH 0.55% = cysteamine hydrochloride; NA = not applicable; QALY = quality-adjusted life-year.

Perspective: CADTH base case.

Appendix 3: Additional Information

Table 6: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and the analysis clear and transparent?		X	
Comments	None		
Was the material included (content) sufficient?		X	
Comments	None		
Was the submission well organized and was the information easy to locate?		X	
Comments	None		

Table 7: Authors information

Authors of the pharmacoeconomic evaluation submitted to CDR

☐ Adaptation of Global model/Canadian model done by the manufacturer

☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

Appendix 4: Reviewer Worksheets

Table 8: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Based on the baseline characteristics of patients upon entry into the CHOC trial, except for an assumed age of entry of 2 years of age and corresponding photophobia score at age 2.[7]	Age of entry into the model is not appropriate as not all patients present with symptomatic corneal cystine crystal deposits at the age of 2. Some patients may be symptomatic and require therapy at a later age, as shown in the CHOC trial.
Efficacy	Based upon data from the OCT-1 and CHOC trials.[7,11] Note: Efficacy for CH 0.55% was applied in the form of no probability of ophthalmic event (i.e., photophobia, visual impairment, band keratopathies, blepharospasm, filamentary keratopathies and corneal vascularization) in the alive state.	The CADTH clinical review noted there was uncertainty with the efficacy of CH 0.55% based on a high risk of bias due to the open-label nature of the trial, as well as serious limitations with the photophobia scales concerning their validity, reliability, and responsiveness. While some benefit compared with 0.1% CH was observed, there was moderate uncertainty in the effect estimates obtained due to the lack of blinding to treatment assignment and the limited evidence of the validity of the IVCM total score, its reliability and lack of an established MCID. Additionally, the long-term effectiveness of CH 0.55% remains uncertain, as the primary end point of the CHOC trial was 90 days, and the single arm OCT-1 trial, which contained data on 8 patients for 60 months, had serious limitations with its efficacy outcomes and no control group, which meant conclusions could not be drawn regarding long-term efficacy of CH 0.55%.[7,11]
Natural history	IVCM score change and probabilities for events including photophobia, visual impairment, band keratopathies, blepharospasm, filamentary keratopathies, and corneal vascularization were obtained from a combination of published literature and clinical expert opinion.	Event rate for filamentary keratopathies beyond age 25 may not be appropriate. In the cited literature, filamentary keratitis decreases from 18% to 13% from the 20-29 to >30 age groups, respectively, while the model assumes a constant proportion of 18% after age 25. Additionally, the clinical expert consulted by CADTH indicated that band keratopathies are unlikely to occur in patients with corneal cystine crystal deposits from cystinosis, and also that such events would not be permanent, contradicting another assumption made by the manufacturer in relation to band keratopathies.
Utilities	Disutility values for photophobia,[5] blepharospasm, band keratopathies, filamentary keratitis, and corneal vascularization were obtained from senior global key opinion leaders.[13] The utility decrements for visual impairment were obtained from a previously published cost-	These values could not be appropriately validated as some of the communications referred to were unavailable when requested from the manufacturer. The value for photophobia was too high and lacked face validity.

Data Input	Description of Data Source	Comment
	effectiveness analysis assessing screening for age-related macular degeneration.[14]	There was an additional issue with the approach used to combine utility values. An additive approach was used, which may overestimate the impact of disutilities compared with a multiplicative approach.
AEs	No adverse events from CH 0.55% or BSC were modelled.	The exclusion of treatment-related adverse events is inappropriate. The product monograph lists eye pain, blurred vision, eye irritation, and eye pruritus among common adverse events with CH 0.55%. In the pharmacoeconomic report submitted by the manufacturer, events related to treatment efficacy are referred to as adverse events. These ophthalmic events are part of the natural progression of cystinosis if left untreated and are thus not adverse treatment events.
Mortality	Canadian life tables[12] adjusted by a standardized mortality ratio such that median survival in all patients would be reached at 40 years of age to be aligned with the typical life expectancy for patients with cystinosis.[13]	Appropriate
Resource Use and Costs		
Drug	NA – the only drug costs included within the model were for the manufacturer submitted drug.	NA
Administration	No administration costs were included.	Appropriate.
Event	Costs and resource use for band keratopathies, blepharospasm, and debridement of filaments were based on feedback from a key opinion leader.[5] Costs related to visual impairment was obtained using the average direct medical and non-medical cost of visual impairment across all stages in Canada[17] and adjusting this by the percentage of the average cost which relates to each level of visual impairment[18] to obtain impairment severity specific costs.	Unclear how costs for blepharospasm, band keratopathies, and debridement of filaments in the Canadian context were derived. The key opinion leader cited is based out of a hospital in France, and it is unclear if the costs/resource use listed in the manufacturer's report and model are from this setting, or are applicable to the Canadian health care system. The costs related to visual impairment included non-medical costs (including productivity losses and dead weight losses from transfers including welfare payments and taxation forgone) which should not be included in the public health care payer perspective, and given patients not on treatment are more likely to be visually impaired, this potentially biases costs against best supportive care.
AEs	As described above, no treatment-related adverse events were included within the model.	Not appropriate, as described above.
Health state	Additional background resource use and associated costs were applied for	Appropriate

Data Input	Description of Data Source	Comment
	ophthalmologist visits according to a key opinion leader,[15] with costs obtained from the Ontario Schedule of Benefits and Physician Services.[16]	

BSC = best supportive care; CH = cysteamine hydrochloride; IVCM = in vivo confocal microscopy; MCID = minimum clinically important difference; NA = not applicable.

Table 9: Manufacturer's Key Assumptions

Assumption	Comment
Model structure, which included two health states (alive and dead) appropriately captured the underlying clinical or biological process.	Not appropriate. The model structure did not appropriately capture the underlying clinical disease pathway.
100% compliance with CH 0.55% is assumed in the base case.	Not appropriate. The clinical experts consulted by CADTH indicated 100% compliance would not occur in clinical practice and that this value would be much lower.
No adverse events were experienced in patients on CH 0.55%.	Not appropriate. Adverse events due to treatment were observed within the pivotal clinical trials, are listed in the product monograph, and should have thus been incorporated in the model.
An annual increase of 0.1 on the IVCM scale was assumed to represent the natural history of disease in the absence of treatment.	This input could not be validated, as it was based on an assumption from a clinical expert and is not based on any clinical data. The clinical review conducted by CADTH noted there was limited evidence for the association of IVCM total score with symptoms.
For patients on treatment, it was assumed IVCM levels would be maintained indefinitely while patients remained adherent to treatment.	There is uncertainty with the estimates of treatment efficacy and stability of effect given issues related to risk of bias in the primary efficacy trial, as well as concerns regarding the outcome measures and lack of control group in the long-term effectiveness.
Patients on treatment and adherent do not experience visual impairment, corneal blindness/vascularization, band keratopathies, and filamentary keratopathies.	There is uncertainty with this assumption, as this assumption was based on stability of IVCM scores in the CHOC trial. The clinical expert consulted by CADTH noted the use of the IVCM total score to predict ophthalmic events is of questionable validity.
No survival benefit from CH 0.55% for ocular cystinosis.	Appropriate
For patients on treatment, it was assumed photophobia levels would be maintained indefinitely while patients remained adherent to treatment.	Appropriate
It was assumed untreated patients would reach extreme (grade 5) photophobia by a specific age with the severity of photophobia increasing linearly over time until the maximum severity is reached at 20 years of age.	Not appropriate. Clinical experts consulted by CADTH indicated there are patients with untreated CCCDs who never reach a grade 5 photophobia severity.

CCCD = corneal cystine crystal deposits; CH = cysteamine hydrochloride; IVCM = in vivo confocal microscopy.

Manufacturer's Results

Table 10: Summary of Manufacturer's Base Case Results

	Total Life-Years	Total Costs	Incremental Cost of CH 0.55%	Total QALYs	Incremental QALYs of CH 0.55%	Incremental Cost per QALY
BSC	11.92	$714,216		11.92		
CH 0.55%	23.70	$2,630,341	$1,916,126	23.70	11.77	$162,755

BSC = best supportive care; CH 0.55% = cysteamine hydrochloride 0.55%; QALY = quality-adjusted life-year.

Source: manufacturer's pharmacoeconomic submission.[4]

Table 11: Manufacturer's Scenario Analyses (Deterministic Analyses)

Parameter	Scenario	Resulting ICUR ($/QALY)
Base case	*Not applicable*	*$165,841*
Treatment effect on visual impairment	Equivalent to IVCM effect	$224,524
Treatment effect on visual impairment	No treatment effect on visual impairment	$280,674
Age everybody has impaired vision (untreated)	20	$153,858
Age everybody has impaired vision (untreated)	40	$183,400
Population	Mixed	$343,048
Change in IVCM without treatment	No increase	$161,635
Grade 5 photophobia by age	30	$180,513
Treatment effect on the incidence of AEs	Equivalent to IVCM effect	$178,867
Blepharospasm incidence (without treatment)	27%	$161,663
Band keratopathies incidence (without treatment)	0%	$178,192
Filamentary keratitis incidence (without treatment)	0%	$164,225
CYSTADROPS compliance	95%	$166,699
1 grade disutility of photophobia	0	$243,412
CYSTADROPS compliance (non-compliant patients)	0%	$172,696
Disutility of band keratopathies	0	$178,171
Disutility of filamentary keratitis	0	$164,069
Reduction in frequency of ophthalmology visits with CYSTADROPS	0%	$161,810
% of impairment leading to corneal blindness	10%	$156,999

AE = adverse event; ICUR = incremental cost-utility ratio; IVCM = in vivo confocal microscopy; QALY = quality-adjusted life-year.

Source: manufacturer's pharmacoeconomic submission.[6]

CADTH Common Drug Review Reanalyses

CADTH undertook a series of scenario analyses as identified in the main body of the report – the results are reported in Table 12 below.

Table 12: Results of CADTH Scenario Analyses

	Scenario	Treatment	QALYs	Cost	ICUR ($ per QALY)
a	Initial patient starting age set to 2 years of age, lifetime time horizon	BSC	16.59	$470,311	
		CH 0.55%	20.84	$2,683,156	$520,360
b	Initial patient starting age set to 2 years of age, 20-year time horizon	BSC	11.39	$122,580	
		CH 0.55%	13.33	$1,688,692	$808,969
c	Compliance set to 100%	BSC	10.20	$596,108	
		CH 0.55%	12.78	$2,300,328	$660,318
d	Compliance set to 50%	BSC	10.20	$596,185	
		CH 0.55%	12.31	$2,333,914	$825,576
e	Disutility for each grade of photophobia is 0.05 instead of 0.025	BSC	7.95	$596,155	
		CH 0.55%	11.85	$2,313,564	$439,573
f	Grade 5 photophobia is reached after 50 years instead of 20	BSC	10.76	$596,084	
		CH 0.55%	12.50	$2,312,571	$985,025

BSC = best supportive care; CH 0.55% = cysteamine hydrochloride 0.55%; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-years.

In the manufacturer's submission, when the population is set to mixed, patients have a photophobia score of 4.40 at age 17. This does not align with the score of 1.77 in the CHOC trial for this same population. In the CADTH base case, the appropriate score of 1.77 was applied at age 17, and the formulas for rate of increase were then applied for all subsequent calculations.

CADTH undertook an exploratory analysis in an attempt to address uncertainty with the coding of the photophobia score for patients on CH 0.55% in the manufacturer's original submission when the population starting age was set to "mixed." The results using the manufacturer's original values (1.37 at baseline, 4.40 at age 17) are presented in Table 13.

Table 13: CADTH Exploratory Analysis

Scenario	Treatment	QALYs	Cost	ICUR ($ per QALY)
CADTH base case with manufacturer's submitted values for photophobia score at age 17	BSC	10.20	$596,347	
	CH 0.55%	11.43	$2,314,957	$1,400,916

BSC = best supportive care; CH 0.55% = cysteamine hydrochloride 0.55%; ICUR = incremental-cost-utility ratio; QALY = quality-adjusted life-year.

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